International Journal of Cardiology 272 (2018) 102–107

Contents lists available at ScienceDirect

International Journal of Cardiology

journal homepage: www.elsevier.com/locate/ijcard

Differential multivariable risk prediction of appropriate shock versus competing mortality - A prospective cohort study to estimate benefits from ICD therapy

Leonard Bergau [a], Rik Willems [b], David J. Sprenkeler [c], Thomas H. Fischer [a], Panayota Flevari [e], Gerd Hasenfuß [a,f], Dimitrios Katsaras [e], Aleksandra Kirova [a], Stephan E. Lehnart [a,f], Lars Lüthje [a], Christian Röver [g], Joachim Seegers [a,h], Samuel Sossalla [a,h], Albert Dunnink [c], Rajevaa Sritharan [a], Anton E. Tuinenburg [d], Bert Vandenberk [b], Marc A. Vos [c], Sofieke C. Wijers [c,d], Tim Friede [f,g], Markus Zabel [a,f,*]

[a] University Medical Center Göttingen, Dept. of Cardiology and Pneumology, Göttingen, Germany
[b] University Hospitals of Leuven, Leuven, Belgium
[c] University Medical Center Utrecht, Dept. of Medical Physiology, Utrecht, Netherlands
[d] University Medical Center Utrecht, Dept. of Cardiology, Utrecht, Netherlands
[e] Attikon University Hospital, Dept. of Cardiology, Athens, Greece
[f] DZHK (German Center for Cardiovascular Research), partner site Göttingen, Göttingen, Germany
[g] University Medical Center Göttingen, Dept. of Medical Statistics, Göttingen, Germany
[h] Division of Cardiology, Dept. of Internal Medicine II, University Hospital Regensburg, Regensburg, Germany

ARTICLE INFO

Article history:
Received 6 April 2018
Received in revised form 18 June 2018
Accepted 27 June 2018
Available online 28 June 2018

Keywords:
Implantable cardioverter defibrillator
Risk factors
Mortality
Sudden cardiac death

ABSTRACT

Background and objective: We prospectively investigated combinations of risk stratifiers including multiple EP diagnostics in a cohort study of ICD patients.
Methods: For 672 enrolled patients, we collected history, LVEF, EP study and T-wave alternans testing, 24-h Holter, NT-proBNP, and the eGFR. All-cause mortality and first appropriate ICD shock were predefined endpoints.
Results: The 635 patients included in the final analyses were 63 ± 13 years old, 81% were male, LVEF averaged 40 ± 14%, 20% were inducible at EP study, 63% had a primary prophylactic ICD. During follow-up over 4.3 ± 1.5 years, 108 patients died (4.0% per year), and appropriate shock therapy occurred in n = 96 (3.9% per year). In multivariate regression, age ($p < 0.001$), LVEF ($p < 0.001$), NYHA functional class ($p = 0.007$), eGFR ($p = 0.024$), a history of atrial fibrillation ($p = 0.011$), and NT-pro-BNP ($p = 0.002$) were predictors of mortality. LVEF ($p = 0.002$), inducibility at EP study ($p = 0.007$), and secondary prophylaxis ($p = 0.002$) were identified as independent predictors of appropriate shocks. A high annualized risk of shocks of about 10% per year was prevalent in the upper quintile of the shock score. In contrast, a low annual risk of shocks (1.8% per year) was found in the lower two quintiles of the shock score. The lower two quintiles of the mortality score featured an annual mortality <0.6%.
Conclusions: In a prospective ICD patient cohort, a very good approximation of mortality versus arrhythmic risk was possible using a multivariable diagnostic strategy. EP stimulation is the best test to assess risk of arrhythmias resulting in ICD shocks.

1. Introduction

More than one decade ago, ICDs have been shown to improve survival in patients at risk of sudden cardiac death (SCD) [1–4]. However, a large number of ICD patients never receive appropriate shocks or die prior to an appropriate ICD therapy [5]. The DANISH trial revealed that ICD therapy does not reduce mortality in patients with non-ischemic cardiomyopathy [6]. As an explanation it was suggested that improvements in interventional and pharmacological therapies have led to steep reductions of mortality over the past decades [7, 8]. In the aftermath, American ACC/AHA/HRS guidelines for ICD treatment were renewed unchanged in 2017 while ESC guidelines have not been updated. ESC and EHRA have, however, proposed the randomized RESET-SCD trial to reassess the effects of primary prophylactic ICD therapy in ischemic cardiomyopathy [9]. Conceptually, any form of ICD therapy can only prevent sudden and tachyarrhythmic mortality, not that from heart failure or non-cardiac causes [10]. As found in the recently presented VEST trial, a scarcity of life-threatening arrhythmias coincides with lack of an effect

* Corresponding author at: University Medical Center Göttingen, Heart Center, Dept. of Cardiology and Pneumology, Robert-Koch-Str. 40, 37075 Göttingen, Germany.
E-mail address: markus.zabel@med.uni-goettingen.de (M. Zabel).

https://doi.org/10.1016/j.ijcard.2018.06.103

of the defibrillator on a primary endpoint of SCD and appropriate shocks (http://www.acc.org/education-and-meetings/image-and-slide-gallery/media-detail?id=80e18113234d4268ab85c328b83c3029). Identification of patient subgroups with significant mortality benefit from ICD therapy remains critical [11, 12], and additional risk stratifiers beyond LVEF need to be implemented clinically [13–15]. To date, few studies investigated risk markers of ICD shocks. Most were focused on microvolt T-wave alternans (MTWA) and had equivocal results [16–19]. A substantial number of potentially useful parameters of risk stratification, for instance electrophysiological and electrocardiographic markers, parameters from cardiovascular history, biomarkers, and possible combinations thereof have been underused [13–15]. We set out to conduct a large prospective cohort study to test different combinations of these risk factors to predict the risk of ICD shocks versus the competing risk of mortality.

2. Methods

2.1. Study design and baseline testing

A prospective international clinical study was initiated as part of the European Union Seventh Framework funded large-scale cooperative project EUTrigTreat. The rationale, objectives and design of the study including statistical plan and sample size calculations have been published previously [20]. In brief, the study enrolled a contemporary ICD cohort to test multiple carefully selected risk markers of clinical relevance for prediction of mortality and arrhythmias. In order to represent a large range from lower to higher risks of appropriate ICD shocks, the inclusion criteria featured ICD patients with primary or secondary prophylactic guideline indications and age ≥ 18 years. The study was registered (NCT01209494) and approved by all participating local ethics boards. Baseline assessments included medical and cardiovascular history, measurement of LVEF, non-invasive or invasive programmed ventricular stimulation (PVS), exercise and atrial paced microvolt T-wave alternans (MTWA) testing, recording of a 12 lead standard ECG and 24-h Holter (for analysis of heart rate variability, heart rate turbulence, number of premature ventricular complexes and non-sustained runs of ventricular tachycardia), and serum biomarkers (high-sensitivity C-reactive protein [hs-CRP], N-terminal-pro B-type-natriuretic protein [NT-proBNP], and serum creatinine). Expecting a wide range of indications and clinical characteristics, ICD programming recommendations were agreed between sites but final programming was left to the discretion of the treating physician [20].

2.2. Programmed ventricular stimulation

The large majority of patients (91%) underwent non-invasive PVS via their implanted ICDs. In case of first ICD implantation, an EP study was done invasively in 60 (9%) patients. A validated abbreviated stimulation protocol with three extrastimuli was used [21]. Inducibility of sustained ventricular arrhythmia was defined as induction of a single monomorphic VT lasting for 30 s or two polymorphic VT/VF episodes requiring cardioversion.

2.3. MTWA testing

MTWA exercise testing (Cambridge Heart, Tewksbury/MA, USA) was performed if patients were in sinus rhythm. When the patient was unable to exercise, atrial pacing was used to increase the heart rate. MTWA tests were graded according to A and B rules [22] by two blinded investigators each from the enrolling and core centers. In case of disagreement, the enrolling center decided the final grade. For analysis, positive and indeterminate results were grouped as non-negative.

2.4. Holter monitoring

A 24 h Holter monitoring was performed using standard devices (Delmar Reynolds Pathfinder, Spacelabs Healthcare, Snoqualmie, WA; Spiderview, Sorin Group, Paris, France; GE Mars, GE Healthcare, Milwaukee/WI, USA). In case of sinus rhythm and < 15% ventricular or atrial pacing, heart rate variability was analyzed using the respective Holter software submodules. Heart rate turbulence and deceleration capacity were calculated using dedicated software (Librasch Calc, V1.02, Schneider R & Schmidt G, TU Munich, Germany).

2.5. Outcomes: all-cause mortality and first appropriate ICD shock

The primary endpoint was all-cause mortality [20]. First appropriate ICD shock was selected as a key secondary endpoint. This endpoint did not include antitachycardic pacing [20]. Patients were followed every 3 to 6 months. If ICD shocks occurred, EGM data were forwarded to the endpoint committee (A.T., R.W., M.Z.) for adjudication.

2.6. Statistical analysis

Cox regression analysis was implemented as described [20]. Death was considered a censoring event using competing risk adjustments [23]. Risk models for shock and mortality were developed using forward selection among a set of known potential risk factors. Adjusting for these, factors were identified that indicated an incremental risk in univariate analyses ($p < 0.05$). Models were then determined through an exhaustive search through combinations of identified risk factors by minimization of the Bayesian Information Criterion [24]. Using score values, patients were subdivided into three groups at low (lowest two quintiles), intermediate (intermediate two quintiles) and high risk (upper quintile). In 148 patients, NT-proBNP was extrapolated from BNP measurements [25]. Discriminatory power of scores was evaluated using area under the ROC curve (AUC) at a prediction horizon of 2 and 6 years [26]. Bootstrapping (generating 1000 samples) was used to estimate the bias introduced by validating the model from the same data used to develop the score [27]. Kaplan-Meier probabilities were compared using the log-rank test. All computations were performed using the R environment for statistical computing and graphics (http://www.r-project.org). Continuous values are expressed as mean +/− standard deviation. p-Values are two-tailed, a level of 5% are considered statistically significant. Correlations are evaluated using Pearson's correlation coefficient.

3. Results

3.1. Patient characteristics

From January 2010 to April 2014, we enrolled 672 ICD patients in four centers. Of 672 patients enrolled, 635 were finally included in the analysis (see Figure DIB1 in [4]). The first ICD was implanted 3.8 ± 3.9 years (median 2.9 years) prior to enrolment, 60 (9%) received their implant at enrolment, 63% (n = 400) had primary prophylactic indications. Mean age was 63 ± 13 years, 81% were male. Mean LVEF was 40 ± 14%. Basic rhythm was sinus rhythm in 510 patients (80%), atrial fibrillation (AF) in 76 patients (12%), and pacemaker rhythm or higher degree AV block in 49 patients (8%). Baseline parameters are shown in Table 1. A single-chamber ICD was implanted in 45%, dual-chamber ICD in 34%, and biventricular ICD in 21%. All patients had VT and VF zones programmed, with lower and upper boundaries of 344 ± 40 ms, and 276 ± 40 ms at baseline, respectively. A mean of 5.3 ± 2.2 ATPs were programmed before a shock in the VT zone. ATP before shock was programmed in the VF zone in 298 patients (48%).

3.2. ECG and Holter parameters

An intrinsic QRS complex was recorded in 535 patients, an RV paced rhythm in 40, a biventricular paced rhythm in 57, in 3 patients QRS classification was not possible. Mean QRS duration of intrinsic complexes was 129 ± 35 ms, mean QT and QTc were 449 ± 52 ms and 459 ± 47 ms, respectively. Mean heart rate on Holter was 67 ± 10 bpm. The number of premature ventricular complexes averaged 2361 ± 5885 per 24 h. The number of non-sustained VT episodes averaged 2 ± 15 per 24 h, and 146 patients (23%) had at least one salvo of non-sustained VT. Not all patients in sinus rhythm (n = 510) were analyzable for heart rate variability and HRT. Absence of the necessary PVCs for HRT analysis occurred in 55 cases. Additional reasons for inability to analyze were > 15% atrial pacing, <66% analyzability for heart rate variability, other technical difficulties, or implausible data. The mean standard deviation of normal-to-normal intervals (SDNN) was 113 ± 43 ms; mean square root of mean of squared differences between normal-to-normal RR intervals (RMSSD) was 31 ± 27 ms; mean heart rate turbulence onset was −0.13 ± 2.12%, heart rate turbulence slope was 5.50 ± 5.09 ms/R-R interval, and deceleration capacity (DC) was 2.12 ± 6.58 ms, respectively.

3.3. EP study and MTWA

An EP study including programmed stimulation was done in 617 patients (97%). Sustained VT/VF was induced in 124 (20%) patients. Monomorphic VT was induced in 81%, polymorphic VT in 11%, and VF in 8%, respectively. Mean cycle length of induced VT/VF was 277 ± 55 ms. MTWA gradings were available for final analysis in 493 patients (97%) with sinus rhythm. Of these, 347 (70%) were performed under exercise, another 146 (30%) via atrial or biventricular stimulation. According to A rules, 28% (n = 140) were graded positive, 51% (n = 249) negative, and 21% (n = 104) indeterminate, respectively. Following B rules, 28%

Table 1
Clinical baseline characteristics for all patients (n = 635), surviving patients (n = 527), and deceased patients (n = 108).

	All (n = 635)	Alive (n = 527)	Deceased (n = 108)	p-Value
Age (years)	63 ± 13	61 ± 13	71 ± 9	<0.001*
Male sex	513 (81%)	420 (80%)	93 (86%)	0.141
Body mass index (kg/m^2)	28.1 ± 5.3	28.3 ± 5.4	27.2 ± 4.7	0.0740
LVEF (%)	40 ± 14	42 ± 14	33 ± 11	<0.001*
DCM	214 (34%)	164 (31%)	50 (46%)	<0.001*
CAD without STEMI	157 (25%)	119 (23%)	38 (35%)	
CAD with STEMI	107 (17%)	93 (18%)	14 (13%)	
Idiopathic VT/VF	46 (7.2%)	45 (8.5%)	1 (0.9%)	
HCM/HOCM	38 (6.0%)	37 (7.0%)	1 (0.9%)	
Brugada	11 (1.7%)	10 (1.9%)	1 (0.9%)	
LQT	8 (1.3%)	8 (1.5%)	0 (0%)	
ARVC	7 (1.1%)	7 (1.3%)	0 (0%)	
CPVT	2 (0.3%)	2 (0.4%)	0 (0%)	
other	45 (7.1%)	42 (8.0%)	3 (2.8%)	
NYHA class				
I	188 (30%)	179 (34%)	9 (8%)	<0.001*
I–II	83 (13%)	71 (13%)	12 (11%)	
II	182 (29%)	148 (28%)	34 (31%)	
II–III	82 (13%)	59 (11%)	23 (21%)	
III	100 (16%)	70 (13%)	30 (28%)	
NT-proBNP (ng/L)	1361 ± 2203	1051 ± 1787	2562 ± 3094	<0.001*
hs-CRP (mg/L)	3.8 ± 5.2	3.4 ± 5.0	5.4 ± 6.0	<0.001*
AF				
Permanent	80 (13%)	48 (9.2%)	32 (30%)	<0.001*
Paroxysmal	137 (22%)	110 (21%)	27 (26%)	
No history of AF	405 (65%)	359 (69%)	46 (44%)	
Intrinsic QRS width (ms)	129 ± 35	126 ± 34	143 ± 35	<0.001*
ß-blockers	470 (85%)	390 (85%)	80 (86%)	0.874
Class I antiarrhythmic drug	11 (2.1%)	10 (2.2%)	1 (1.1%)	1.000
Class III antiarrhythmic drug	153 (28%)	127 (28%)	26 (30%)	0.795
Digitalis glycosides	81 (15%)	52 (12%)	29 (33%)	<0.001*
Oral anticoagulation	191 (35%)	141 (31%)	50 (56%)	<0.001*

AAD = anti-arrhythmic drug, AF = atrial fibrillation, ARVC = arrhythmogenic right ventricular dysplasia, CM = cardiomyopathy, hs-CRP = high sensitivity C-reactive protein, LVEF = left ventricular ejection fraction, NT-proBNP = n-terminal pro brain natriuretic peptide; NYHA = New York Heart Association.
* = significant.

(n = 138) were positive, 57% (n = 282) negative, and 15% (n = 73) indeterminate, respectively.

3.4. Occurrence of endpoints

Over a follow-up of 4.3 ± 1.5 years, 96 (15.1%) patients received a first appropriate shock (annualized rate 3.9% per year). The cycle length of the primary arrhythmia leading to appropriate shock in a VT/VF episode was 255 ± 48 ms (minimum 170 ms, maximum 650 ms), 47% (n = 45) were delivered in the VF zone. Overall mortality was 17.0% (n = 108, annualized rate 4.0% per year), and adjudicated as cardiac in n = 30 (58%), n = 17 (32%) deaths were classified as non-cardiac. Classification of the mode of death was not possible in 5 cases.

3.5. Risk prediction for mortality and appropriate shock and associated risk scores

3.5.1. Univariate predictors of mortality

Univariate Cox regression revealed age, LVEF, estimated glomerular filtration rate (eGFR), NYHA functional class, history of AF, ischemic heart disease, COPD, NT-pro-BNP, hs-CRP, non-negative MTWA, deceleration capacity (DC) and several parameters of HRT as strong clinical predictors of mortality (see Table DIB2 in [4]). Strong predictors of mortality from Holter monitoring were deceleration capacity (DC), heart rate turbulence category, turbulence onset (TO), and turbulence slope (TS). From the 12 lead ECG, QRS width and QTc predicted mortality.

3.5.2. Univariate predictors of appropriate shock

Univariate clinical predictors of appropriate shock were LVEF, eGFR, COPD, NT-pro-BNP, intrinsic QRS, intrinsic QTc, and secondary prophylactic indication (see Table DIB3 in [4]). Non-negative MTWA was a univariate predictor of appropriate shocks, the hazard ratio was 1.85 (CI 1.18–2.92, p = 0.007) for A rules, and 1.73 (CI 1.11–2.69, p = 0.015) for B rules, respectively. None of the Holter parameters were predictive of shock. In general, there were less significant predictors for shock as compared to mortality, and p-values were less significant.

3.5.3. Inducibility at EP study: univariate prediction

Inducibility at EP study was a significant predictor for appropriate shocks but not for mortality. Inducibility at EP study predicted appropriate shock similarly in patients with ischemic (HR 2.13, CI 1.15–3.92, p = 0.0155) or non-ischemic cardiomyopathies (HR 2.03, CI 1.10–3.76, p = 0.0233), primary (HR 2.25, CI 1.24–4.09, p = 0.0080), or secondary prophylactic indication (HR 1.98, CI 1.07–3.68, p = 0.0294), respectively.

3.5.4. Multivariate risk models and risk score

The final mortality model (Table 2) involved 563 patients and 102 deaths, with 8% (n = 53) missing values for NT-pro-BNP and 25% (n = 148) imputed values based on BNP [25]. Missing values for all other parameters were below 3% with the exception of hs-CRP (25%). The final appropriate shock model was based on 602 patients (Table 2). The respective risk scores are shown in Table DIB4 in [4]. Multivariate predictors of mortality were age, LVEF, NYHA functional class, eGFR, history of AF, and NTpro-BNP. Multivariate predictors of appropriate shock were LVEF, secondary prophylaxis, and inducibility at EP study. MTWA A rules missed inclusion in the multivariate shock model (p = 0.058), eGFR was only of borderline significance in the final model (p = 0.070). The risk score for prediction of all-cause mortality featured a c-index of 0.811 (CI 0.757, 0.866) at 2 years, and 0.865 (CI 0.764, 0.966) at 6 years. The c-index for prediction of shock using the Fine and Gray model was 0.725 (CI 0.634, 0.815) at 2 years of FU, and 0.691 (CI 0.612, 0.771) at 6 years, respectively. In a subgroup of primary prophylactic patients, statistically significant predictors identified in multivariate analyses including all patients for mortality (age, LVEF, NYHA) and shock (LVEF, inducibility) were very similar and had similar HR.

3.5.5. Individualization of risks: cumulative incidence curves by quintiles

In general, risk separation was excellent, as shown in Fig. 1. A wide and very individual risk continuum was found for both risks. For instance, the lowest mortality quintile showed zero mortality and the lower two mortality quintiles a combined annual risk of <0.6% (Fig. 1A). In the overall cohort, the lower two quintiles of patients (40%) of each respective risk exhibited very low risks (Fig. 1A and B).

3.5.6. Correlation between risk scores

The risk of appropriate shock did not match well with the risk of all-cause mortality, as the sub-classification of low, intermediate, and high risk groups for each endpoint shows (Fig. 2). Accordingly, the correlation between mortality score and shock score was only moderate (see Figure DIB5 in [4]) with an r^2 of 0.31 (r = 0.56, p < 0.001), i.e. 69% of their variation explained by other factors.

4. Discussion

4.1. Main findings

This prospective study in a large ICD patient cohort with guideline-based indications for ICDs in primary and secondary prevention of SCD aimed to identify a differential multivariate risk stratification strategy targeted at predicting either mortality or ICD shocks. To our knowledge, this is the first head-to-head comparison of multiple diagnostic risk factors for this particular aim of predicting ICD shocks in comparison to all-cause mortality. We showed that a very good approximation

Table 2
Multivariate hazard ratios for prediction of all-cause mortality and appropriate shock.

n = 635	Hazard ratio		95% confidence interval		p-Value	
	Mortality	Shock	Mortality	Shock	Mortality	Shock
Age (per 10 yrs)	1.73		1.37–2.19		<0.0001*	
LVEF (per 5%)	0.80	0.92	0.73–0.87	0.80–0.95	<0.0001*	0.0018*
History of AF	1.69		1.13–2.54		0.0110*	
NT-pro-BNP (100 ng/L)	1.46		1.15–1.84		0.0017*	
NYHA functional class (>II)	1.73		1.16–2.58		0.0072*	
eGFR (per 30 mL/min)	0.70	0.77	0.52–0.95	0.58–1.02	0.0236*	0.0700
Secondary prophylaxis		1.98		1.29–3.04		0.0017*
EP inducibility		1.86		1.19–1.90		0.0067*

Open field = not selected as model variable; AF = atrial fibrillation; eGFR = estimated glomerular filtration rate; EP = electrophysiological; LVEF = left ventricular ejection fraction; NT-proBNP = n-terminal pro brain natriuretic peptide, NYHA = New York Heart Association.
* Significant.

of the risk of ICD shocks versus total mortality was possible after development of differential risk scores. For the prediction of all-cause mortality, a typical selection of parameters showed high accuracy. For prediction of ICD shocks, inducibility at EP study was an excellent, specific and independent clinical test in addition to LVEF, it was not associated with all-cause mortality. For individual patients, higher mortality risk did not necessarily represent higher appropriate shock risk, and vice versa. Different combinations of mortality and shock risk suggest different ICD survival benefit, which could be assessed when the implantation of an ICD is considered.

4.2. Predictors of outcomes including shocks in ICD patients

In univariate analysis, we confirmed typical risk factors for mortality in our ICD cohort of 635 patients (and with an excellent c-index). The only multivariate factor predicting both shock and mortality was LVEF, which corroborates its importance as a risk stratifier in ICD patients. Risk factors for mortality have been described in very large ICD registries [28, 29] as well as heart failure registries [30, 31], and were fully confirmed in our study. Only few studies have reported predictors of ICD shock, but rather predictors of presumed arrhythmic mortality or SCD. Our data demonstrates that risks of mortality and shock have to be considered separately in ICD recipients. Lee et al. [32] recently reported simultaneous shock and mortality predictors from baseline variables, however, they did not perform additional diagnostic testing and the number of identified patients with a presumed low ICD benefit was <10% of patients. We found similar hazard ratios regarding prediction of appropriate shock, for instance for eGFR as the best clinical baseline shock predictor in our study. Adding specific EP diagnostic tests, we showed that EP stimulation and MTWA outperformed the baseline parameters, and the group of patients that could be defined to have marginal ICD benefits as well as a clearly high benefit was considerably larger than in the paper by Lee et al. [32]. The value of Holter parameters to predict appropriate shock was clearly disappointing. We identified a group of 40% of our patients (two quintiles) characterized by a low annual appropriate shock rate of ≈1.8%. This shock rate can be translated to a risk of SCD <1.0% per year had the patient not been implanted an ICD [33]. We also identified a large group of ≈20% of all patients who had a predicted ≈11% annual shock rate associated with low to intermediate mortalities of ≈3–9%, likely resulting in a very high ICD benefit. In between these two well defined groups with low (≈40% of patients) or high (≈20% of patients) shock risk, there is still a large number of patients with intermediate combinations of the two risks calling for individualization of risk versus benefit of the ICD in a given patient. On this part, our study is hypothesis-generating and needs confirmation. As expected, secondary prophylaxis was identified as an independent predictor of shocks, underscoring the good indication of ICD therapy in these patients. As MTWA and heart rate turbulence cannot be assessed in AF, we derived additional models applicable only to patients in sinus rhythm. In the respective model for appropriate shock, MTWA closely missed the final model ($p = 0.058$). Thus, it was possible to calculate a final shock model with variables that were available in all patients. Similarly, for mortality, there was also one final model for all patients, as there was no independent parameter measurable only in sinus rhythm. Our prediction models do have implications for assessment of individual ICD benefit which is further detailed in [4].

4.3. Predictive value of EP study versus MTWA in ICD patients

We showed that EP and MTWA testing do have value for the identification of arrhythmic risk in an individual patient. Indeed, upon univariate analysis, we found both tests to be good predictors of appropriate shock with HR of 2.15 for inducibility at EP study ($p = 0.0009$) and 1.85 for MTWA ($p = 0.007$). In general, predictors for shock were less common as compared to predictors of mortality. In the multivariate model for shock, inducibility at EP study had a HR of 1.86 ($p = 0.007$) and was the only diagnostic test specific for the prediction of appropriate shock. In comparison, MTWA ($p = 0.058$) missed inclusion in the multivariate model. Our results are in line with the ABCD trial [19] where EP study and MTWA were directly compared. From our data, PVS is clearly recommended over MTWA when estimating the risk of appropriate shock in an ICD patient. EP stimulation has been historically recommended to assess the risk for malignant ventricular arrhythmias [34, 35] in case of the need for risk stratification. It has been involved in the first evidence-based indications for prophylactic ICD therapy [36–38]. EP stimulation was by far the best diagnostic test for shock prediction in our study. This is in line with its proven value in assessing risk of SCD in patients after myocardial infarction and with ischemic cardiomyopathy [38–40] as well as other guideline indications. Its value was similarly high in non-ischemic cardiomyopathy patients. MTWA as a non-invasive test failed to be considered for the final multivariate model.

4.4. Future outlook

After publication of the DANISH study, European ICD guideline indications require an update including this landmark trial [6]. Meanwhile, ESC and EHRA have proposed the RESET-SCD trial, a randomized trial reassessing the benefit of primary prophylactic ICD therapy in ischemic cardiomyopathy, without additional risk stratification [9]. We are convinced that the overall group of ischemic cardiomyopathy patients may contain patients that derive clear benefit from the ICD, as identified by subgroups of significant size in the current study. New randomized studies should therefore enroll patients with presumed borderline survival benefit from ICD therapy. For identification, risk markers such as those from our current study could be utilized. The data of large observational ICD studies such as the prospective EU-CERT-ICD-study (NCT 02064192) and the Dutch DO-IT study [41] will become available in the second half of 2018 and can also influence the design of future randomized trials.

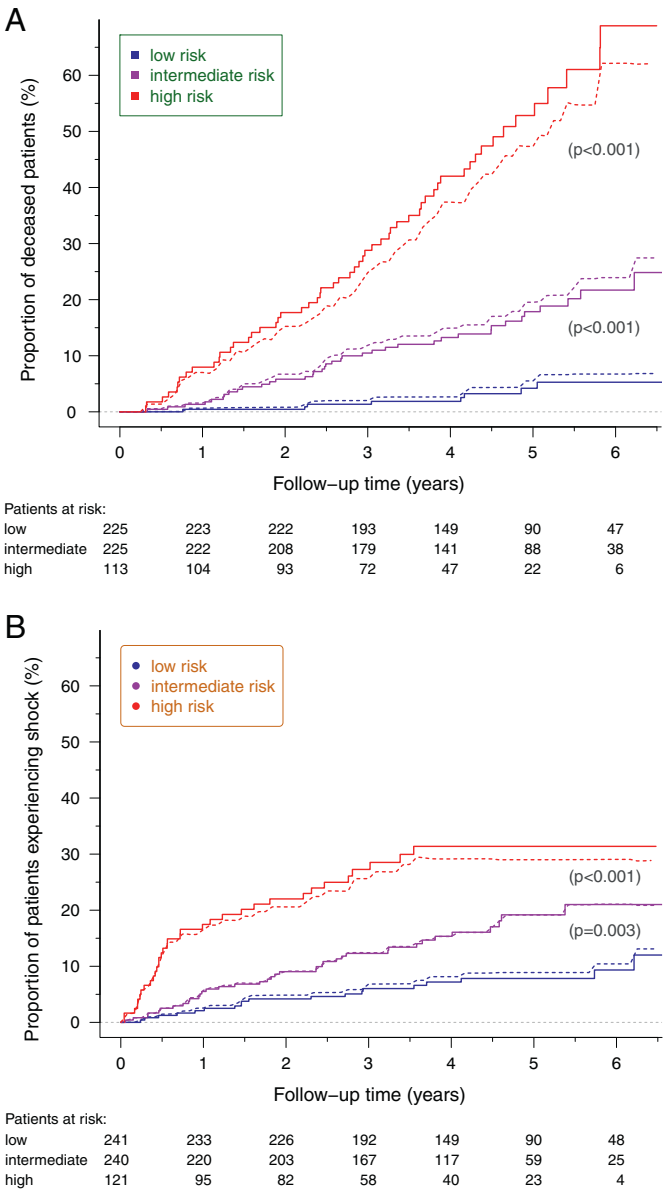

Fig. 1. Cumulative event-probability curves for mortality and appropriate shock (Panel A and B). For each risk, the cohort is divided into three risk groups (low: two quintiles, intermediate: two quintiles, high: one quintile), the calculation is provided by separate risk scores for all-cause mortality and appropriate shock. The dashed lines indicate the cumulative event-probabilities after bootstrap bias correction. **Panel A**: The mortality risk score provides excellent separation of low, intermediate, and high mortality risks. The low risk mortality group (two quintiles) shows an annualized risk of 0.5%. In contrast, the high risk mortality group (one quintile) features an annual risk of 11%. Within the latter patients, it can be expected that non-sudden cardiac deaths or non-cardiac deaths compete with the occurrence of ventricular arrhythmias. In particular, patients with a low predicted shock risk may not improve their prognosis wearing an ICD. **Panel B**: The appropriate shock risk score provides good separation of low, intermediate, and high shock risks. The low risk shock group, a large group covering two quintiles and a number of 241 patients, has an average annual risk of 1.8%. Since a first appropriate shock does not always correspond with SCD (if the patient had not had an ICD) but only in 30–50%, this number corresponds to an SCD rate < 1%/yr. In patients with an estimated SCD rate < 1% annually, depending on age and other mortality factors independent of arrhythmias, omission of an ICD may be discussed. In contrast, the high risk group for shock (one quintile) features an average annual risk of ~8.5%, well qualifying the patient for an ICD with high survival benefit. In the intermediate risk of shock group (two quintiles), the risk is still ~4% annually, corresponding to maybe a 2% annual SCD rate. Therefore, patients in the intermediate risk group for shock, should probably also obtain an ICD as they derive ICD benefit, unless a very high competing risk of non-arrhythmic mortality can be seen from the mortality score.

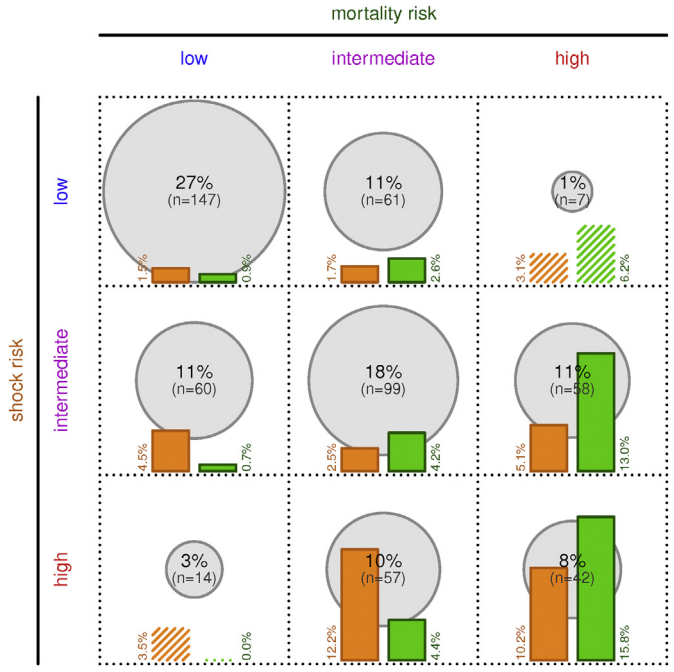

Fig. 2. Distribution of patients to combinations of risk categories (low, intermediate, high) and their associated annualized mortality and shock risk. Grey circles denote the frequencies of patients in the various categories. The orange and green bars denote the actual annualized shock and mortality risks in a category, respectively. For each risk, the cohort is divided into three risk groups (low: two quintiles, intermediate: two quintiles, high: one quintile), resulting in nine subgroups, of which seven have significant size. Annualized shock risk is found to be >10% per year in the highest quintile of the shock score and can coincide with both an intermediate (4.4% per year) and a high (10.2% per year) mortality. Annualized mortality risk is found to be >10% per year in the highest quintile of the mortality score and can coincide with both an intermediate (5.1% per year) and a high risk of appropriate shock.

4.5. Limitations

There are several limitations of our study. We included patients with primary or secondary prophylactic indications and not necessarily undergoing de novo implantation, with the intent that the results apply to all ICD patients, and also late in their follow-up. Inclusion of 672 patients in four centers was consecutive regarding screening from the outpatient clinics. A common reason to opt for non-participation in the study was the EP stimulation with possible induction of arrhythmias. In the majority of patients, EP stimulation was done via ICD and from a single site. Noninvasive EP study has been described in other studies [42], and the diagnostic yield appears to be very similar to its invasive counterpart. Despite the simplified approach, EP stimulation was clearly the best diagnostic test to predict appropriate shock, and could not be replaced by MTWA or other risk stratifiers. Our predefined endpoint was appropriate ICD shock, it did not include antitachycardic pacing. It cannot be ruled out that some antitachycardic pacing episodes were clinically useful for the patient. The study group was convinced from the outset that antitachycardic pacing episodes would overestimate life-saving effects of the ICD [43]. In the meantime, this was supported by the MADIT-RIT results where the conventional arm was treated with a large number of ATP but outcomes such as shock or mortality were not improved [44]. Finally, we had a recommended, not mandatory ICD programming, which might have potentially biased the number of appropriate shocks.

5. Conclusions

Prospective and comprehensive risk stratification in a typical cohort of ICD patients achieved very accurate approximation of both mortality and ICD shock risk. Appropriate shock risk and all-cause mortality diverge in

large subgroups. Different combinations of multivariate predictors were identified that differentiate the presumed individual ICD benefit.

Among the available diagnostic tests, EP stimulation was an excellent predictor of shock risk not relating to all-cause mortality.

Funding

The research leading to the results has received funding from the European Community's Seventh Framework Programme FP7/2007–2013 under grant agreement No. HEALTH-F2-2009-241526, EUTrigTreat, and No. HEALTH-F2-2009-602299 EU-CERT-ICD. G.H., T.F. and S.E.L. are principle investigators of the German Center for Cardiovascular Research (DZHK), partner site Göttingen. R.W. is supported as a postdoctoral clinical researcher by the Fund for Scientific Research Flanders (FWO).

Conflicts of interest

None.

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